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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,786	04/11/2001	David J. Diller	1073.060A	4635

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EXAMINER

ZHOU, SHUBO

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,786	DILLER ET AL.	
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 11-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 11-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Amendment

The amendment to the claims filed 7/5/05 is not in complete compliance with 37 CFR 1.121(c) because claim 12 contains text that is lined-through but the claim status indicates “previously presented.” Clarification and correction are requested.

Claims 1-5 and 11-17 are currently pending and under consideration.

The rejection of claims 6-10 under 35 USC 112, second paragraph in the previous Office action is hereby withdrawn in view of the cancellation of the claims.

CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly added claims 16-17 recite “counting the number of ligands in at least one cluster and rating complementarity of the combinatorial library to the target molecules based at least in part on the count.” This limitation is considered as new matter because the specification does not provide adequate description for the limitation. Applicants assert that paragraphs [0087] and [0088] of the specification provide support for the limitation. However, the two paragraphs describe clustering analysis but not “counting the number of ligands in at least one cluster and rating complementarity of the combinatorial library to the target molecules based at least in part on the count.”

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 11-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1994) in view of Rarey et al. (J. Mol. Biol., 1996).

This rejection is reiterated from the previous Office action for reasons as set forth in the previous Office action from page 4, paragraph 9 to page 8, paragraph 22.

Ho et al. describes that the various compound databases have inherent strengths and weaknesses (assessing) with regard to particular chemical classes (clustering). Further, an initial database of fragments is necessary, ligand diversity is assured through the combinatorial assortment of building blocks (page 214, left column, lines 11-15, and lines 33-37), as in instant claim 1, lines 1-4. Ho et al. describes the "common core" as defined in the instant specification, page 5, paragraph 21.

Ho et al. state that "fragments must be screened and edited to ensure steric and electrostatic complementarity. . . To accomplish this, all structures would have to be considered in regard to all bond loci in space as well as the structures and pharmacophoric elements associated with them" (page 214, left column, lines 43-46). By setting this constant distance to the radius of a molecular atom type, steric contacts are revealed where penetration of the receptor molecular surface by the ligand vector model occurs (see page 214, right column, last line, to page 215, left column, line 4). In the generation of fragments for the chain_dbase database the structures were docked in the active site with the appropriate orientation (page 216, left column, last paragraph), as in instant claim 1, lines 5-8.

However, Ho et al. does not describe the limitation of determining the RMS deviation, forming clusters, and rating based on the clusters formed.

Rarey et al. describes a method for screening larger sets of ligands for their binding affinity to a given receptor (page 472, left column, lines 21-23). The ligand is divided into fragments. The base placement algorithm finds positions of the base fragment in the active site (page 474, left column, lines 18-31). The second step in the base placement algorithm is to cluster the placements according to an appropriate distance function such as rms deviation between two placements (page 475, left column, lines 33-37). Rarey et al. uses a hierarchical clustering algorithm as applied to rms deviations (page 477, right column). A binding mode closely approaching the experimental geometry is predicted among the few highest-ranking placements (page 472, left column, lines 23-26), as in instant claim 1, lines 9-15, and claim 2.

Rarey et al. further, describe the use of a cubic grid covering three-dimensional space aligned to the Cartesian coordinate axis. The grid is for checking a ligand atom for overlap with the receptor by inspecting the receptor atoms whose centers (center of mass) are located in all cubes intersecting a sphere centered in the ligand atom (page 476, left column, line 57, to right column, line 10). The distance between placements is the rms deviation between the coordinates of the ligand (rms threshold 0.7Å) (page 477, right column, lines 39-45), as in instant claim 3.

Rarey et al. describes via the images in Figures 8 and 9, for each protein-ligand interaction, a pair of matching points (hot spots) is generated resulted from searching for new interactions (page 476, right column, Searching for new interactions section). Further, Rarey et al. describes the docking procedure comprising FLEXX analyzing the structure of the ligand and detects local topological symmetries at single bonds whose torsion angle can be changed. The computation of rms deviations also considers this local symmetry (page 478,

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left column, The ligand section), and the receptor has defined coordinates and crystalline position (fixed) (478, left column, The receptor section), as in instant claim 5.

Rarey et al. implements the FLEXX docking tool on a SUN SPARC station 20 (page 486, left column, Summary of results), as in instant claims 6-8, 10-13, and 15.

Since Ho et al. describes the improvement to meet the needs necessary for understanding receptor ligand binding for novel drug development (page 2 13, left column, Introduction section), and Rarey et al. describes the increasing interest in automatic screening of ligand databases by computational methods in the drug discovery process (page 470, Introduction section, columns 1-2), one of ordinary skill in the art at the time the invention was made would have been motivated by Ho et al. to develop improvements directed to understanding receptor ligand binding for novel drug development as taught by Rarey et al. Thus, it would have been obvious to one of skill in the art to use the method, system and program for assessing a combinatorial library as taught by Ho et al. and Rarey et al. including docking, clustering analysis and

Applicants' argument filed 7/5/05 has been fully considered but is not found persuasive. Applicants argue that neither of the cited references disclose forming clusters of multiple ligands and rating complementarity of a combinatorial library based on the clusters. This is not found persuasive because, as admitted by applicants (page 7 of the response), Rarey et al. disclose cluster formation in the context of clusters of different placements of selected fragments of a single ligand. Further, as also admitted by applicants (page 7 of the response), Rarey et al. imply that the method can be repeated for several ligands in a set of ligands. This clearly indicates that Rarey et al. at least suggest using clustering on multiple ligands. By the

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nature of clustering, the members in the cluster would be automatically ranked and thus rated. As set forth above, Ho et al. state that "fragments must be screened and edited to ensure steric and electrostatic complementarity. . . To accomplish this, all structures would have to be considered in regard to all bond loci in space as well as the structures and pharmacophoric elements associated with them." These fragments are interpreted as being multiple ligands, i.e. members of a library. One of ordinary skill in the art would have then been motivated by Rarey et al. to use the clustering methods for multiple ligands. Applicants further argue that Ho et al. do not disclose docking multiple ligands. This is also not persuasive because, as discussed above, docking multiple fragments of a ligands disclosed by Ho et al. is interpreted as multiple ligands because each fragment is a potential ligand for the target, which is the basis for docking the fragments of a ligands.

Claims 4 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1 994) in view of Rarey et al. (J. Mol. Biol., 1996), as applied to claims 1-3, 5, 11-13, and 15 above, further in view of Aldenderfer et al. (1984).

This rejection is reiterated from the previous Office action.

As applied to claims 1-3, 5, 11-13, and 15 above, Ho et al. discloses a method and a system to search for complementary components in a chemical library and Rarey et al. discloses a method for ranking ligands based on rms deviations. Rarey et al. describes the advantages and disadvantages to using hierarchical clustering algorithm as applied to rms deviations. However, Ho et al. and Rarey et al. do not disclose the limitation of forming clusters using a single linkage-clustering algorithm.

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Aldenderfer et al. provide a review of hierarchical clustering methods including single-linkage clustering algorithm (page 38-40), as in claims 4 and 14. Aldenderfer et al. state that single-linkage clustering bases on similarities of one member to existing members and its major advantage is its invariance to monotonic transformations of the similarity matrix and it is unaffected by ties in the data. See page 38, the bridging paragraph of pages 38-39. One of ordinary skill in the art would have been motivated by Aldenderfer et al. to modify the methods of Ho et al. and Rarey et al. to use single-linkage clustering to take its advantage of being unaffected by ties in the data so that other unrelated factors would not affect the clustering results.

Applicants do not separately provide arguments for this rejection, but rather argue together with the rejection of claims 1-3, 5, 11-13, and 15 above. The argument is on the same ground as that provided for the rejection of claims 1-3, 5, 11-13, and 15. The argument is not persuasive for the same reasons as set forth above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136 (a). A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136 (a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than six months from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete

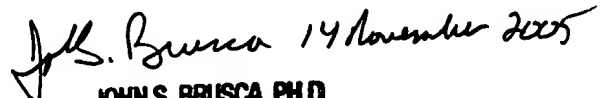
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Shubo (Joe) Zhou, Ph.D.



Patent Examiner

 14 November 2005
JOHN S. BRUSCA, PH.D.
PRIMARY EXAMINER